REMARKS

The Applicants have added Claims 65 and 66. Support for Claim 65 is found in the Applicants' Specification on page 22, lines 17 – 24 and page 33, lines 11 – 20. Support for Claim 66 is found in original Claims 1 – 14 and in the Applicants' Specification on page 8, line 19 through page 10, line 6. No new matter has been added.

Claim 64 stands rejected under 35 U.S.C. §112, first paragraph.

The Applicants respectfully submit that the Specification provides clear support for the subject matter of Claim 64, which recites a process for reducing fibroses. More specifically, the Specification discloses that the properties of RGTA are characterized by its unique effects on the quality and rate of the tissue repairs. This is described in the Applicants' Specification on page 14, lines 14 – 18. "These effects are manifested by an almost complete reconstitution and identity with the original tissue structure (prior to the lesion) and by the almost complete absence of cicatricial traces such as in particular signs of fibroses or loss of its structural integrity." Moreover, the Applicants' Specification also discloses on page 16, lines 15 – 19, emphasis added, that the AXY polymers of Claim 64 demonstrate "[a]n antifibrotic activity which is manifested *in vitro* and *in vivo* by regulatory effects on the proliferation of mesenchymal cells such as the smooth muscle cells, fibroblasts or hepatic cells and the quality of the type of collagen that they secrete, as well as an activity on the phenotypic quality of the collagens synthesized by these cells and by the notable reduction in the fibrotic cicatricial sequelae." Thus, the Applicants' Specification clearly provides the requisite written description for claiming a process for reducing fibrosis. Therefore, the Applicants respectfully request that rejection of Claim 64 be reconsidered and withdrawn.

Claims 42 and 61 – 64 stand rejected under 35 U.S.C. §112, first paragraph. The Office Action states that the Specification enables the *in vitro* use of RGTA 1005, 1010, 1012, 1013, 1112 and 1113 for treating factors involved in fibrosis, but does not reasonably provide enablement for treating fibroses with all other AXY polymers. The Office Action further alleges that the Specification speaks only on the *in vitro* administration of polymers of the series RGTA 1000 – 1025 and 1110 – 1115 to observe their effect on growth kinetics in smooth muscle tissue cultures, as well as the synthesis of collagens, but that the Specification does not provide actual guidance or evidence supporting the use of the AXY polymer in treating or reducing fibroses in human or animal models.

The Applicants respectfully submit that *in vitro* tests are typically utilized as the starting point for new therapeutics and proof of efficacy *in vivo* and are now considered as standard by one of ordinary skill in the art and regulatory authorities. This is demonstrated by the enclosed Papy-Garcia Declaration, paragraph 12. For example, the Applicants' Specification on page 2, lines 13 – 18 cites French Patent No. 2,718,025 (the "'025 patent"). In the '025 patent, the anti-inflammatory activity of HBGFPP (which constitutes another class of polymers) was studied *in vitro* and confirmed *in vivo*. With respect to the issue of product safety, regulatory authorities now request *in vitro* assays in the field of genotoxicity as noted in the Papy-Garcia Declaration, paragraph 12. For cosmetic products, animal assays are forbidden in Europe under a new regulation. In another example, efficacy for anti wrinkle agents is supplied with *in vitro* assays on skin fibroblast showing increases of collagen synthesis. The use of *in vitro* data to ascertain *in vivo* effects is thus well established for one of ordinary skill in the art as shown in the Papy-Garcia Declaration, paragraph 12. In the field of growth factors and their uses as wound healing agents or for colony stimulating factors or for interleukin, the efficacy of the growth factor for *in*

vivo uses are measured routinely by *in vitro* assays. This is also shown in the Papy-Garcia Declaration, paragraph 12. Thus, one of ordinary skill in the art understands that demonstration of safety and efficacy must be provided through *in vitro* assays.

The Applicants' AXY polymers are selected on the basis of stabilizing, potentiating and protecting growth factors such as FGFs or TGF beta. To one of ordinary skill in the art, this indicates that AXY regulates the activity of the growth factors which are involved in the fibrosis formation and will reduce fibrosis *in vitro*. The Papy-Garcia Declaration, paragraph 12 demonstrates this. It is therefore a reasonable expectation for one of ordinary skill in the art that the claimed polymers will obtain the same effect *in vivo*. In any event, the Applicants' Specification at page 15, lines 3 – 4 and page 16, lines 15 – 23 clearly indicates that antifibrotic activity of the polymers of Claims 42 and 61 – 64 is manifested *in vitro* and *in vivo* and is based on known characteristic effects of the activity, particularly the regulatory effects on the proliferation of the mesenchymal cells and the quality and quantity of secreted collagens.

In addition, Examples 12 and 13 and Figs. 23 – 26 of the Application presents *in vitro* data which shows that the claimed AXY polymers inhibit the growth of fibrosis-forming cells such as smooth muscle cells, fibroblasts or hepatic cells, and restore the quantity and quality of collagen produced by such cells under conditions expected to induce fibrosis (*e.g.*, radiation) to that of control cells. One of ordinary skill in the art would interpret these data to mean that administration of the claimed AXY polymers would produce the same effect on fibrosis-forming cells *in vivo*, thereby confirming the efficacy of the AXY polymers in reducing fibroses *in vivo* as a treatment will involve only routine experimentation. This is seen in the Papy-Garcia Declaration, paragraph 12.

The Applicants' model was well known in the art at the time of filing the application. This is indicates that only routine experimentation would be necessary from one skilled in the art. The Applicants' Specification includes several working examples of *in vitro* experiments, *e.g.*, Examples 12 and 13, that represent strong guidance to the skilled artisan that the AXY polymers according to Claims 42 and 61 – 64 reduce fibroses. Thus, there is every reason to believe that this activity would also occur in an *in vivo* experiment. For example, Example 12 uses HISM cells (Human Intestinal Smooth Muscle cells). As discussed in Example 12 (Applicants' Specification on page 52, lines 4 – 9), fibroses are characterized by an increase in type III collagen, which is associated with an increase, but to a lesser degree, in the ratio between type III collagen and type I collagen. Another collagen, type V collagen, is associated with the quality of the organization of the collagen fibers in the matrix, *i.e.*, the fibrillogenesis. In fibrotic tissues, the decline in the levels of type V collagen is one of the origins of the loss of structure of the collagen fibers of the extracellular matrix. The use of HISM cells in studying fibrosis is exemplified by "Collagen Synthesis by Human Intestinal Smooth Muscle Cells in Culture," Graham et al., Gastroenterology, Volume 2, Number 2, pages 400-5 (Feb. 1987). Graham discusses the synthesis of collagen by HISM cells in culture. Graham et al. states that the types of collagens synthesized by these cells in vitro were the same as those extracted from strictured human bowel. The HISM cells were used to elevate the effects of radiation on cellular survival and the induction of fibrotic phenomena analyzed by means of the quantity and quality of the types of collagen secreted by these normal cells or in an inflammatory situation or in the repair process by fibrosis. Therefore, based on the guidance found in the Applicants' Specification, along with the knowledge in the art as exemplified by Graham et al. (which has a relatively simple design), one skilled in the art would need only minimal, routine experimentation to

confirm that the AXY polymers would produce the same effect on fibrosis-forming cells *in vivo*. Such routine experimentation certainly does not constitute "undue" experimentation for a rejection under §112. Therefore, Applicants respectfully request that rejection of Claims 42 and 61 – 64 be reconsidered and withdrawn.

Claims 42 and 61 – 64 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Office Action alleges that the skilled artisan cannot envision all variations of the AXY polymer allowable, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of synthesis of all AXY polymers. The Office Action further alleges that only the use of polymers following the synthesis methods as described in the Specification (example, the first dextran carboxymethylation step addressed on page 30), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

The Applicants understand the rejection to have acknowledged that the Specification teaches one skilled in the art how to make and use AXY polymers where A is -(O-CH_2-CH_2-CO)- or glucose; X is -COOH or –COO^-Na^+; and Y is -CO-CH_2-CHOH-CH_2-SO_3H, -CO-CH_2-CHOH-CH_2-$SO^{3-}Na^+$, -SO_3H or -$SO^{3-}Na^+$.

However, the Applicants respectfully submit that the Specification provides the necessary written description for one skilled in the art to readily envision the full array of AXY polymers encompassed by Claims 42 and 61 – 64.

The full range of polymers encompassed by Claims 42 and 61 – 64 can be made by the disclosed synthetic schemes or by employing routine techniques known to one skilled in the art as shown in the Papy-Garcia Declaration, paragraph 11. The Applicants' Specification discloses

that the AXY polymers can contain –(O-CH_2-CH_2-CO)- or any sugar as the A component, and one of ordinary skill in the art would understand that any sugar could be readily substituted into the disclosed synthetic schemes without significantly altering the reaction chemistry.

With specific regard to group A in the AXY polymers, the Application discloses A as a monomer, which can be identical or different, selected from the group consisting of sugars, esters, alcohols, amino acids and nucleotides. See the Applicants' Specification on page 7, lines 11 – 15. The Papy-Garcia Declaration, paragraph 6, shows that one of ordinary skill in the art would be able to prepare polymers AXY in where A is a sugar unit, (corresponding to any sugar unit, not only glucose, but galactose, xylose, manose, etc.) in a polysaceharide and where A can be different sugars, as in the saccharidic moiety of glycoproteins or in other glycans.

In addition, one skilled in the art, would be able to prepare polymers AXY in where A can also be a molecule bearing alcohols groups, as polyalcohols based on the Papy-Garcia Declaration, paragraph 6. For example, based on Examples 1 and 2 on pages 22 and 29 of the Specification, respectively, show the synthesis of AXY polymers in which A is -(O-CH_2-CH_2-CO)- or glucose. One of ordinary skill in the art could readily envision the specific AXY polymers formed by using sugars other than glucose in the disclosed reaction schemes with little or no modification as set forth in the Papy-Garcia Declaration, paragraph 5. The substitution of other sugars into the synthesis scheme could be readily accomplished with only routine experimentation by one of ordinary skill in the art.

With specific regard to group X, the Application discloses that X represents a carboxyl bearing group (-R--COO--R'), in which R is a bond or an aliphatic hydrocarbon chain, optionally branched and/or unsaturated, and which can contain one or more aromatic rings except for benzylamine and benzylamine stalfonate, and R' represents a hydrogen atom or a cation

(Applicants' Specification on page 6, lines 4 – 8). In accordance with the Papy-Garcia Declaration, paragraph 7, one skilled in the art would be able to make polymers AXY in where X represents a carboxyl bearing group (--R--COO--R') in which R is an alkyl (R = -[CH_2]n, where n≥l), an allyl (R = -CH=CH[CH_2]n, where n≥l), aryl, linear or branched groups and R' is a hydrogen atom or a cation.

With specific regard to group Y, the Application discloses that Y represents a sulfate or sulfonate group bonded to monomer A and is contained within a group according to one of the following formulas: --R--O-SO.sub.3--R', --R- -SO.sub.3--R , --R--SO.sub. 3--R', in which R is a bond or an aliphatic hydrocarbon chain, optionally branched and/or unsaturated, and which can contain one or more aromatic rings except for benzylamine and benylamine sulfonate, and R' represents a hydrogen atom or a cation (Applicants' Specification on page 6, lines 9 – 13). One skilled in the art would be able to make polymers AXY in where Y represents a sulfate group bonded to monomer A according to the following formula: --R--SO.sub.3--R` in which R is a bond, an alkyl (R = -[CH_2]n, where n ≥l) , allyl (R = - CH=CH[CH_2]n, where n≥l), aryl, linear or branched groups as confirmed by the Papy-Garcia Declaration, paragraph 8.

With regard to the additional group Z, the application discloses that Z is a substance different from X and Y, which confers on the polymer additional solubility or lipophilic properties, supplementary biological or physicochemical properties, or a therapeutic or diagnostic agents. The Application states also that Z can be identical or different, and selected from the group consisting of amino acids, fatty acids, fatty alcohols. ceramides or derivatives thereof and nucleotide addressing sequences (Applicants' Specification on page 8, line 19 to page 9, line 2). The Papy-Garcia Declaration, paragraph 9 confirms that one skilled in the art

would be able to make polymers AXYZ in where Z can be identical or different, and selected from the group consisting of amino acids or derivatives thereof.

Thus, one skilled in the art would understand from their own knowledge and the teachings of the Application that substitution of the X, Y, and Z components as claimed would not alter the reaction chemistry as disclosed throughout the Application, and in Examples 1 and 2 described above in particular. Again, the Papy-Garcia Declaration, paragraph 10, confirms this. As a result, the Application contains sufficient teaching to allow one of ordinary skill in the art to make and use the AXY polymers claimed in the Application. Thus, one of ordinary skill in the art would understand that the Applicants had possession of the entire claimed range of AXY polymers as of the Application filing date. Therefore, Applicants respectfully request that the rejection of Claims 42 and 61 – 64 be reconsidered and withdrawn.

Claims 42 and 61 – 64 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard are the invention. In particular, the Office Action alleges that the recited monomer, –(O-CH_2-CH_2-CO)-, is indefinite because it is not clear whether the last O is double bonded to the last C. The Applicants respectfully submit that Figs. 1 and 4 clearly disclose that in the above-recited formula the "CO" are bonded via a double bond. Therefore, Applicants respectfully request that the rejection of Claims 42 and 61 – 64 be reconsidered and withdrawn.

Claim 64 stands rejected under 35 U.S.C. §112, second paragraph, as the phrase "reducing fibroses" is allegedly indefinite because it is not clear what would constitute a reduction in fibroses.

The standard for determining definiteness of a claim term is well settled. To determine if a term is definite, the claim language must be read in light of both the prior art and the

Specification. A claim term is definite if one skilled in the art would understand the scope of the claim when read in light of the Specification.

The Applicants respectfully submit that Examples 12 and 13 are directed to the anti-fibrotic role of the polymers of Claims 42 and 61 – 64 and describes fibrosis and its characteristics. (See Applicants' Specification on page 51, line 1 through page 58, line 24). Fibrotic tissue is a filling tissue, normally transitory, intended to conserve the structural and functional integrity of the organs and tissues. Fibrosis is characterized by the presence of a permanent inflammatory infiltrate, the existence of a disequilibrium in the balance between a proliferative and a quiescent state of the conjunctival or mesenchymal cells such as fibroblasts or smooth muscle cells, the progressive destruction of the invaded tissue which is renewed only slightly or in a defective manner, the existence of a disequilibrium of the balance between the synthesis and the degradation of the extracellular matrix (Applicants' Specification on page 51, lines 4 – 18). A reduction of fibrosis is understood, first, by a diminution of these aforementioned characteristics by comparing the collagen secretion and the phenotype in the presence or absence of the polymers of Claims 42 and 61 – 64 and second, by a reduction in the quantity of fibrosis when the preventative role of the polymers of Claims 42 and 61 – 64.

Thus, the term "reducing fibroses" corresponds to an almost complete reconstitution and identity with the original tissue structure (prior to the lesion) and by the almost complete absence of cicatricial traces as well as an anti-fibrotic activity manifested (at least in part) by the notable reduction in the fibrotic cicatricial sequelae (Applicants' Specification on page 14, lines 14 – 18 and page 16, lines 15 – 19). Therefore, Applicants respectfully request that the rejection of Claim 64 be reconsidered and withdrawn.

The Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

T. Daniel Christenbury
Reg. No. 31,750

TDC:lh
(215) 656-3381